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Three-arm randomized phase II study of carboplatin and paclitaxel in combination with cetuximab, cixutumumab, or both for advanced non-small cell lung cancer (NSCLC) patients who will not receive bevacizumab-based therapy: An Eastern Cooperative Oncology Group (ECOG) study (E4508)

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Abstract

Background—Pre-clinical evidence supports the clinical investigation of inhibitors to the insulin-like growth factor receptor (*IGFR*) and the epidermal growth factor receptor (*EGFR*) alone and in combination in patients with NSCLC.

Patients and Methods—Patients with chemotherapy-naïve, advanced NSCLC and an ECOG performance status (PS) 0/1 were eligible. Patients were randomized to receive: carboplatin AUC 6 iv + paclitaxel 200 mg/m² iv on day 1 every 3 weeks combined with either cetuximab (CET) iv

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weekly (arm A), cixutumumab (CIX) iv every 2 weeks (arm B), or both (arm C). Patients with non-progressive disease (PD) after 12 weeks of therapy were permitted to continue on maintenance antibody therapy until PD. The primary endpoint was progression-free survival (PFS). The design required 180 eligible patients and had an 88% power to detect a 60% increase in median PFS for either comparison (arm A vs C or arm B vs C) using the log-rank test.

Results—From 9/09 until 12/10, 140 patients were accrued. The study was closed to accrual early because of excessive number of grade 5 events reported on arms A and C. Thirteen patients died during treatment (A=6; B=2; C=5), including 9 within approximately 1 month of starting therapy. The estimated median PFS for arms A/B/C were similar at 3.4, 4.2, and 4 months, respectively.

Conclusions—Based upon the apparent lack of efficacy and excessive premature deaths, this study does not support the continued investigation of carboplatin + paclitaxel + CIX alone or in combination with CET in patients with advanced NSCLC.

Introduction

Molecularly targeted agents are becoming an important component of therapy in the management of some patients with advanced non-small cell lung cancer (NSCLC). One of the hallmarks of cancer is the dysregulation of growth signaling pathways (1). Inhibition of the epidermal growth factor receptor (*EGFR*) pathway has been validated in some patients with advanced NSCLC (2). In one phase III study, patients with advanced NSCLC randomized to receive chemotherapy with or without cetuximab, a monoclonal antibody to *EGFR*, demonstrated a modest improvement survival with the addition of cetuximab, although this was not sufficient to lead to regulatory approval (3). Another study of carboplatin plus a taxane with and without cetuximab demonstrated a numerically higher overall survival (p=NS) for the cetuximab-containing arm (4).

In recent years the insulin-like growth factor (*IGF*) has been studied to understand its' role in the development, pathogenesis, and progression of lung cancer. Signaling through the IGF receptor (*IGFR*) pathway occurs primarily through the phosphatidylinositol-3 kinase (*PI3K*)-Akt pathway and the mitogen-activated protein kinase (*MAPK*) pathway, resulting in increased cell proliferation and inhibition of apoptosis (5–7). Deregulation of the *IGF* pathway appears to result in an increased risk of lung cancer, decreased survival in patients with stage I disease, and facilitation of malignant transformation (8–11). Synergistic activity of *IGF-1R* inhibitors and cytotoxic agents has been described, establishing the rationale for combining *IGFR* inhibitors with chemotherapy (12). In addition, outcomes of nude mice bearing A549 NSCLC tumors treated with the anti-IGF-1R antibody h7C10 combined with chemotherapy or the anti-*EGFR* antibody, cetuximab, were superior to those of mice treated with either agent alone (12). The rationale for combining *EGFR* and *IGFR* inhibitors is further supported by additional studies which implicate the expression of *IGF-1R* with a reduced efficacy of anti-*EGFR* targeting, including resistance to gefitinib (13–15). Other pathway activation, including *AKT* signaling, has been associated with resistance to *EGFR* inhibitors (16). Combining *IGF-1R* inhibition with *EGFR* inhibition may reduce this *AKT* pathway activity (16).

Monoclonal antibodies, including the fully human IgG1 antibody Cixutumumab, have been developed to deregulate the *IGF* pathway. In vitro, treatment with Cixutumumab induces apoptosis in human xenograft models and demonstrates increased cytotoxicity when combined with *EGFR* inhibition (17). A randomized phase II study comparing patients treated with chemotherapy +/- *IGFR* inhibition originally reported higher response rates (although subsequently retracted in 2012) for those receiving the anti-*IGFR* therapy (18). Therefore, based upon pre-clinical and early clinical information, we conducted this randomized phase II study to evaluate the efficacy of chemotherapy combined with *EGFR* inhibition or *IGFR* inhibition or both in patients with advanced NSCLC who are not receiving bevacizumab-based therapy.

Patients and Methods

Eligibility

To be eligible, patients must have had a diagnosis of NSCLC, measurable (as defined by RECIST version 1.1) stage IV disease (including M1a and M1b according to the 7th edition of the TNM classification system) or T4NX (stage IIIB) defined by a nodule in the ipsilateral lung lobe, if not a candidate for combined chemotherapy and radiation or surgery. Patients must have not received prior systemic therapy, including bevacizumab, anti-*EGFR* or anti-*IGFR* therapy, for advanced disease. Patients receiving neo-adjuvant or adjuvant chemotherapy were eligible if more than 1 year had passed prior to randomization to this trial. All patients had an ECOG PS of 0 or 1. Patients were not eligible if they had untreated or symptomatic central nervous system (CNS) metastases. Patients with a history of CNS metastases that were both definitively treated and stably controlled were eligible. Patients were also excluded if they had major surgery within 4 weeks prior to randomization, history of interstitial pneumonitis or pulmonary fibrosis, uncontrolled hypertension or cardiac disease, synchronous malignancy within the last 3 years or those thought to be of a low risk for recurrence definitively treated < 3 years prior to randomization, serum fasting glucose of > 120 mg/dL or above the institutional upper limits of normal (ULN) within 2 weeks prior to randomization, poorly controlled diabetes mellitus, history of allergic reactions attributed to compounds of similar chemical or biological composition to cixutumumab, history of arterial thrombosis, pulmonary embolus, deep venous thrombosis or hemorrhagic disorders <28 days prior to randomization, or peripheral neuropathy > grade 1 as per the CTCAE version 4 grading scale. Within 2 weeks prior to randomization, partial thromboplastin time (PTT) < 1.2 × ULN and international normalized ratio (INR) 1.5 was required. Patients must have had normal hepatic, renal, and bone marrow function. Written informed consent was obtained from all participants.

Study Design, Endpoints, and Treatment

This was a multi-center, randomized trial conducted by ECOG. The primary objective was to evaluate the progression-free survival (PFS) of patients with NSCLC randomized to carboplatin plus paclitaxel plus either cetuximab (arm A), cixutumumab (arm B), or both (arm C). The secondary objectives included evaluation of response rate, disease control rate (complete response plus partial response plus stable disease), overall survival, and toxicities. Additional secondary objectives included evaluating EGFR by immunohistochemistry

(IHC), mutation, and gene copy number, *IGF-1R* and *IGF-2R* expression, and *KRAS* mutation. Plasma-based biomarkers were also evaluated for total and free *IGF-1* and *IGF-2*, and *IGF*-growth factor binding protein 3 (IGFBP3).

The treatment schema for this trial is displayed in Figure 1. Each treatment cycle lasted 6 weeks (42 days). Patients were randomized to receive carboplatin AUC=6 i.v. plus paclitaxel 200 mg/m² i.v. on days 1 and 22 of each cycle in combination with either cetuximab 250 mg/m² i.v. days 1, 8, 15, 22, 29, and 36 of each cycle (Arm A) or cixutumumab 10 mg/kg i.v. on days 1, 15, and 29 of each cycle (Arm B), or the combination of cetuximab and cixutumumab (Arm C) at the dose and schedule specified for these therapies on arms A and B, respectively. The loading dose for patients receiving cetuximab was 400 mg/m² i.v. on day 1 of cycle 1 only. After two 6-week cycles of induction therapy, patients who had not progressed continued onto maintenance therapy of cetuximab, cixutumumab, or both corresponding to their treatment assignment per randomization until disease progression or unacceptable toxicity. Imaging studies were conducted at baseline and at each 6 week treatment interval.

Tumor samples were analyzed by immunohistochemistry (IHC; *EGFR*, *IGF-1R* and *IGF-2R* expression), fluorescent in-situ hybridization (FISH; *EGFR* gene copy number) and DNA sequencing (*EGFR*, *KRAS* gene mutations). FISH scores were interpreted according to the Colorado Scoring Criteria (19).

Statistical Considerations

This 3-arm study planned to randomize 180 eligible and treated patients (200 total patients after 10% inflation for ineligibility) over 12 months with 9 additional months of follow-up to compare the combination of cixutumumab and cetuximab (Arm C) to each of the single agents (Arms A and B) without a formal comparison between the cetuximab alone (Arm B) and cixutumumab alone (Arm C) arms. This design had a yield of 88% power to detect a 60% increase in median PFS (5.6 months vs. 3.5 months) for either comparison at the 1-sided 0.10 significance level using the log rank test. Full information would be reached at 108 PFS events in each comparison. There was no plan to compare the experimental arms to each other.

Safety data on patients and a comparison of toxicity rates of each arm was collected and an interim safety analysis was planned among the first 20 patients who completed the initial 3 cycles of treatment. Early stopping rules were defined by 6 or more events of any grade 3 or higher non-hematological toxicity, any grade 4 or higher hematological toxicity, or grade 3 or higher febrile neutropenia or infection with neutropenia.

Archived tissue and serum was obtained from all patients who consented to participate in the exploratory laboratory research studies. Assuming 75% of patients would participate in the correlative studies and have analyzable samples for study, the estimated sample size for the correlative study was 135 patients. For the correlative endpoints to cetuximab (*EGFR* and *K-Ras*) we anticipated that the mutation rate of this population would be 15%. Among the 135 expected samples, 90 of these patients would have received cetuximab and 45 would have been randomized to the cixutumumab alone arm. Therefore, 14 of the 90 patients receiving

cetuximab were expected to have a mutation. Assuming a one-sided type I error rate of 0.10, this sample size provided 81% power to detect a 100% improvement in the median PFS from 3 months in the mutation negative group to 6 months in the mutation positive group among those patients treated with cetuximab. For the correlative endpoints specific to cixutumumab (*IGF-1R* and *IGF-2R*) the anticipated expression rate was assumed to be 50%. Among the 135 expected samples, 90 of these patients will have received cixutumumab. Therefore, 45 of 90 patients receiving cixutumumab were expected to have positive expression levels. Assuming a one-sided type I error rate of 0.10, this sample size provided 96% power to detect a 100% improvement in the median PFS from 3 months in the zero expressing group to 6 months in the expression positive group among those treated with cixutumumab.

Overall survival was defined at the time from randomization to death from any cause, with follow-up censored at the date of last contact. Objective response was evaluated using RECIST 1.1 criteria. PFS was defined to be the time from randomization to death or documented disease progression, whichever occurred first. Patients that were alive at the time of analysis were censored at the date at which they were last known to be alive and progression-free.

Kaplan-Meier curves were used to estimate event-time distributions. Cox proportional hazards model, stratified on gender and histology (squamous vs. non-squamous) were used to estimate hazard ratios and test for significance for PFS. PFS and OS were compared using logrank tests. Adverse events, patient demographics, disease characteristics and response rates were compared using Fisher's exact tests. All p-values are two-sided and confidence intervals are at the 95% level. Correlative studies were conducted using similar analysis methodology.

Results

From September 11, 2009 through December 17, 2010, one-hundred and forty patients were accrued. The study was subsequently terminated on April 11, 2011 due to excessive grade 5 events within 30 days of registration. Table 1 summarizes the patient demographics and disease characteristics. There were no substantial differences between the arms. The majority of patients had male gender and white race, as well as ECOG PS 0 and < 5% weight loss in the previous 6 months. Similar rates of squamous and non-squamous histology were represented. The percentage of patients receiving at least 2 cycles (12 weeks) of therapy were 51%, 69%, and 60% for arms A, B, and C, respectively. The percentage of patients receiving at least 4 cycles (24 weeks) of therapy were 26%, 26%, and 17% for Arms A, B, and C, respectively.

An interim safety analysis was conducted in November 2010 after approximately 20 patients were randomized to each arm and had completed 3 cycles of treatment. At that time, the study was accruing more rapidly than anticipated and a follow-up call was scheduled for December 2010, after more toxicity data had been submitted and further analyses conducted. The study was suspended for excessive grade 5 events within 30 days of registration at that time, on December 17, 2010. A full review of all available data was then conducted and

reviewed, resulting in termination to accrual on April 19, 2011. At the time of the safety analysis, there was found a higher-than-expected rate of adverse events on Arm C, which included deaths for which a treatment-related attribution could not be excluded. In addition, there was a higher-than-expected rate of early deaths on arm A. However, a review of these deaths identified that disease, not treatment-related complications, was the likely cause of death in most of the cases. Therefore, all patients on Arm C discontinued therapy. All patients on Arms A and B may have continued therapy according to the protocol at the discretion of the study participant and the treating physician.

All toxicities, regardless of attribution and including grade 5 events, are summarized in Table 2. In total, 6 deaths were reported on arm A, 3 on arm B, and 5 on arm C. Deaths on Arm A were attributed to asystole in 1 patient, lung infection or respiratory failure in 2 patients, colitis in 1 patient, and unspecified reasons in the other 2. On Arm B, 2 deaths were for unspecified reasons and 1 death was due to cancer. On arm C, 3 deaths were attributed to pulmonary disease (hypoxia, respiratory failure, acute respiratory distress syndrome), and 2 were unspecified. Grade 3/4 neutropenia was reported in 29%, 30%, and 42% for arms A/B/C, respectively; however, grade 3/4 febrile neutropenia was reported in only 7%, 4.5%, and 4.2% for arms A/B/C, respectively. Grade 3/4 hyperglycemia was more common on the cixutumumab-containing arms (14–17%) compared with arm A (2%). In addition, more patients on arm C experienced grade 3/4 hyponatremia (17%) compared with arms A or B (2% and 4.5%, respectively).

At the time of data analysis, 111 of 127 eligible and treated patients had died and a total of 123 patients experienced a PFS event. The median follow-up on patients still alive (n=18) was 31 months. The estimated median PFS and corresponding 95% CI on each treatment arm was 3.4 months (2.6–5.8), 4.2 months (3.5–5.3), and 4 months (3.2–5.4), for arms A, B, and C, respectively (Figure 2). Arm C did not improve PFS compared to arm A (HR 1.12, 95% CI (0.71–1.78), p=0.62) or arm B (HR 1.10, 95% CI (0.71–1.72), p=0.67). The estimated median OS and corresponding 95% CI on each treatment arm was 9.8 months (7.4–17.2), 7.7 months (5.8–11.5), and 8.8 months (7.2–14.9) for arms A, B, and C, respectively (Figure 3). The response rate for arm A, B, and C, were 11%, 22%, and 22%, respectively. The disease control rate for arms A, B, and C, were 47%, 63%, and 63%, respectively.

Results of Exploratory Correlative Studies

This study was underpowered to detect differences in subsets defined by biomarker studies. When *EGFR* was analyzed by FISH, there were 5 failures, while 39 tested negative and 30 tested positive according to criteria described previously (20). The median OS for *EGFR* negative and positive (by FISH) was 8.6 months (95% CI 6.4–12) and 9.5 months (95% CI 6.8–26.7), respectively, log rank p=0.06. There was no difference in these groups' PFS (log rank p=0.18); similarly, no differences were observed by whether or not cetuximab was received.

For *EGFR* mutation status, exons 18–21 were evaluated but no mutations were found except in 5 patients harboring an exon 19 mutation. No significant differences were observed in their outcomes compared to those without mutation.

KRAS genotyping was conducted, and the numbers of patients tested was too small for statistical testing. For codon 12.34, 72 patients had the GG genotype, while 7 had the GT genotype, 1 had GC, 4 had GA, and 1 had TT. For codon 12.35, 8 patients had the GC genotype, while 73 had the GG genotype; 2 had the GA genotype and 1 had the GT genotype. For codon 13.38, 5 patients had the GA genotype, while 79 had the GG genotype. For codons 61.182 and 61.183, all patients had the AA genotype. A total of 23 patients (among 85) had a mutation in any of the above mentioned codons, but comparisons of OS and PFS were not significant.

IHC studies reported no significant differences when compared by treatment arm or by group when the protein expression was dichotomized as positive (≥ 200) and negative using the H-score system (21). Median *IGF-1R* score was 190 (range 30–390); median *IGF-2R* score was 145 (range 20–350); median *EGFR* membrane and cytoplasm H score was 190 (range 0–380); and median *EGFR* membrane H scores was 160 (range 0–390).

Discussion

Results from this randomized, open-label, multi-institutional, phase II study do not support continued evaluation of cixutumumab in combination with carboplatin plus paclitaxel with or without cetuximab in the patient population studied. The study did not meet its primary endpoint of demonstrating improved PFS with the cixutumumab-containing regimens compared with carboplatin plus paclitaxel plus cetuximab regimen. While response rates and disease control rates trended higher with the 2 cixutumumab-containing arms compared with the carboplatin/paclitaxel/cetuximab arm, neither PFS nor OS appeared superior with the cixutumumab-containing arms. Patient characteristics were similar between 3 arms with the exception of more active smokers in the cetuximab + cixutumumab-containing arm. Disease characteristics were also similar between each arm. A few toxicity differences were noted between the arms. More grade 3 hyponatremia was observed in the cetuximab-cixutumumab-containing arm and, as expected, more grade 3 and 4 hyperglycemia was reported in the cixutumumab-containing arms. While more grade 3/4 neutropenia was reported on the cetuximab-cixutumumab-containing arm there was no difference in febrile neutropenia or infection rates amongst the arms.

The trial was closed prior to planned accrual goals due to concerns about excessive grade 5 events reported for arm A and C. A detailed analysis of each death did not demonstrate a clear pattern of causality. Excessive grade 5 events had not been previously reported in larger phase III trials of chemotherapy with cetuximab, including in combination with carboplatin and paclitaxel (3, 4). While excessive grade 5 events were not reported on arm B, accrual was halted based on a consensus opinion of the leaders of the study, including ECOG members as well as members of NCI/CTEP. Reasons for this decision included the recently reported negative phase III study with figitumumab (monoclonal antibody targeting the insulin-like growth factor-1 receptor), which failed to confirm the promising results reported in the randomized phase II study (22). Our study was designed prior to knowing the results of the phase III trial with figitumumab (22). In that trial, the DSMC recommended early closure due to futility, but also excessive toxicity, including 5% grade 5 events in the figitumumab arm.

Biomarker studies are an integral component of trials assessing molecularly targeted therapy. While unselected patient populations may not benefit from a given targeted therapy, correlation of outcomes with molecular targets may identify a subpopulation of patients likely to benefit. The best examples to date in NSCLC include the identification of *EGFR* mutations that predict response to *EGFR* tyrosine kinase inhibitors and *ALK* gene rearrangements, which predict response to *ALK* tyrosine kinase inhibitors (23–25). Unfortunately, biomarker studies (which were exploratory and presumably compromised further due to early study closure) of the current trial did not provide additional insights into subgroups of patients who may benefit from cixutumumab-containing regimens.

In vitro and in vivo studies supported the clinical testing of combination studies of *IGF-1R* and *EGFR* dual inhibition (11, 12). Results from a phase I/II study of erlotinib in combination with cixutumumab in patients with advanced NSCLC (most had received 1 or more prior regimens) was reported by Weickhardt et al in 2012 (26). Patients were treated in a dose-escalation manner (3+3 design). The most frequent AE's were fatigue, rash, diarrhea, anorexia, and nausea. Of 18 patients evaluated, 5 achieved stable disease, including 1 patient who had SD for > 14 months. There appeared to be little activity in an unselected *EGFR*-wild type patient population. Biomarker analysis on this small study demonstrated a trend towards benefit in PFS for patients with the highest quartile of baseline free IGF-1.

In the first line setting Karp et al initially reported promising results from a randomized phase II study of carboplatin plus paclitaxel plus or minus figitumumab (antibody to *IGFR*) (18). Since this initial report, results from this study were published in 2009, but subsequently retracted in 2012, when the sponsor learned that the overall response rate and PFS data was incorrect (27,28). Additionally, a phase III study of figitumumab in combination with carboplatin plus paclitaxel in a non-adenocarcinoma patient population, failed to demonstrate increased efficacy with the addition of figitumumab (22). In this trial, 681 patients were enrolled, most of whom had squamous cell cancer (86%). The HR crossed the pre-specified futility boundary of 1.1 favoring paclitaxel and carboplatin alone. In those with low baseline IGF levels, safety, tolerability, and survival appeared worse with the addition of figitumumab to carboplatin and paclitaxel.

In conclusion, treatment with cixutumumab in combination with carboplatin plus paclitaxel with or without cetuximab does not appear to improve PFS or OS in the unselected patient population tested in our study. Prior studies, as detailed above, hypothesize the level of circulating IGF levels may impact therapies that block *IGFR* activity. Future studies, if any are to be conducted in NSCLC, should only be conducted if a biomarker, such as high circulating IGF levels, is used to select potentially responsive patients.

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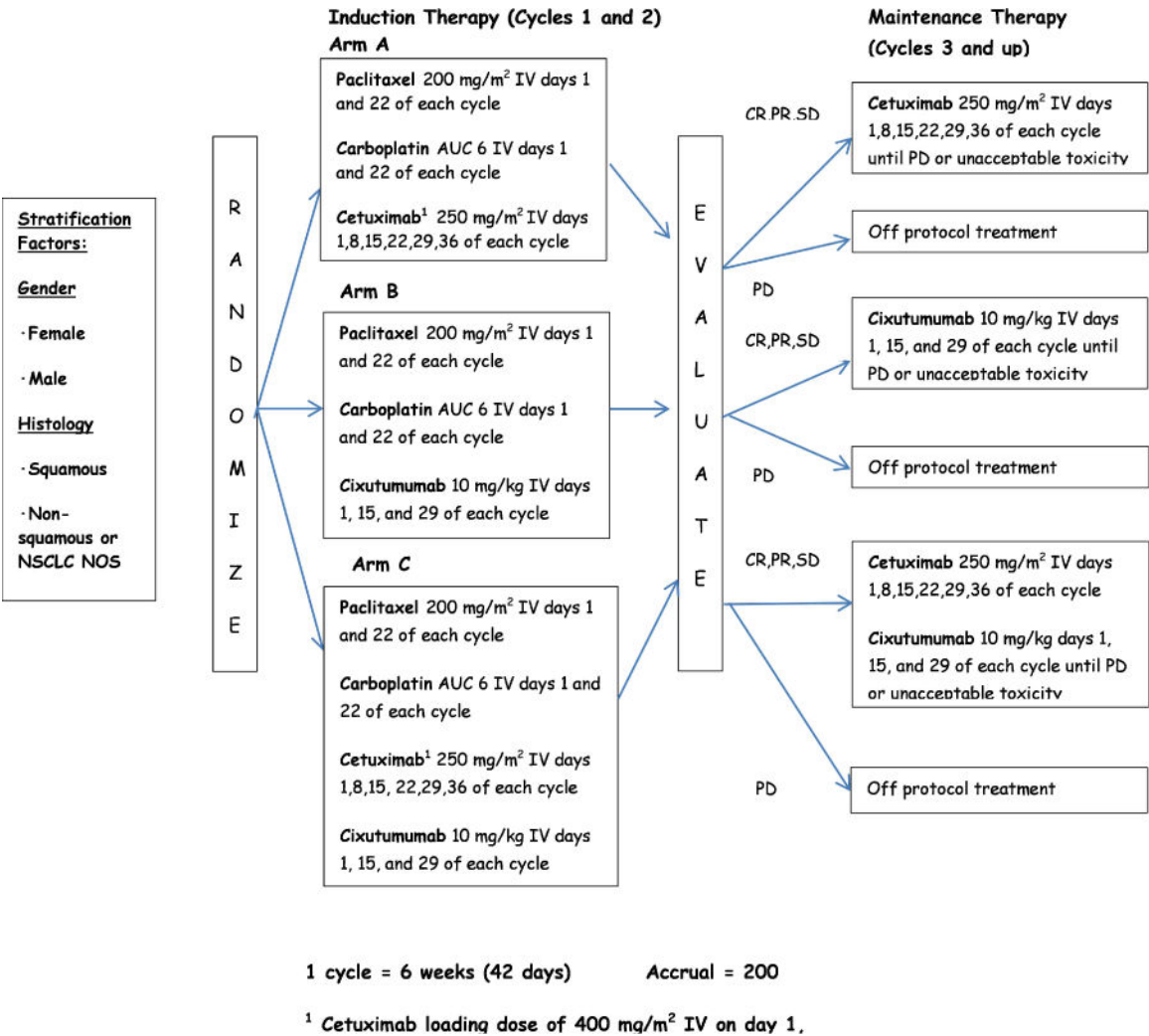


Figure 1. E4508 Schema
This figure provides the treatment regimen, schedule, and stratification factors

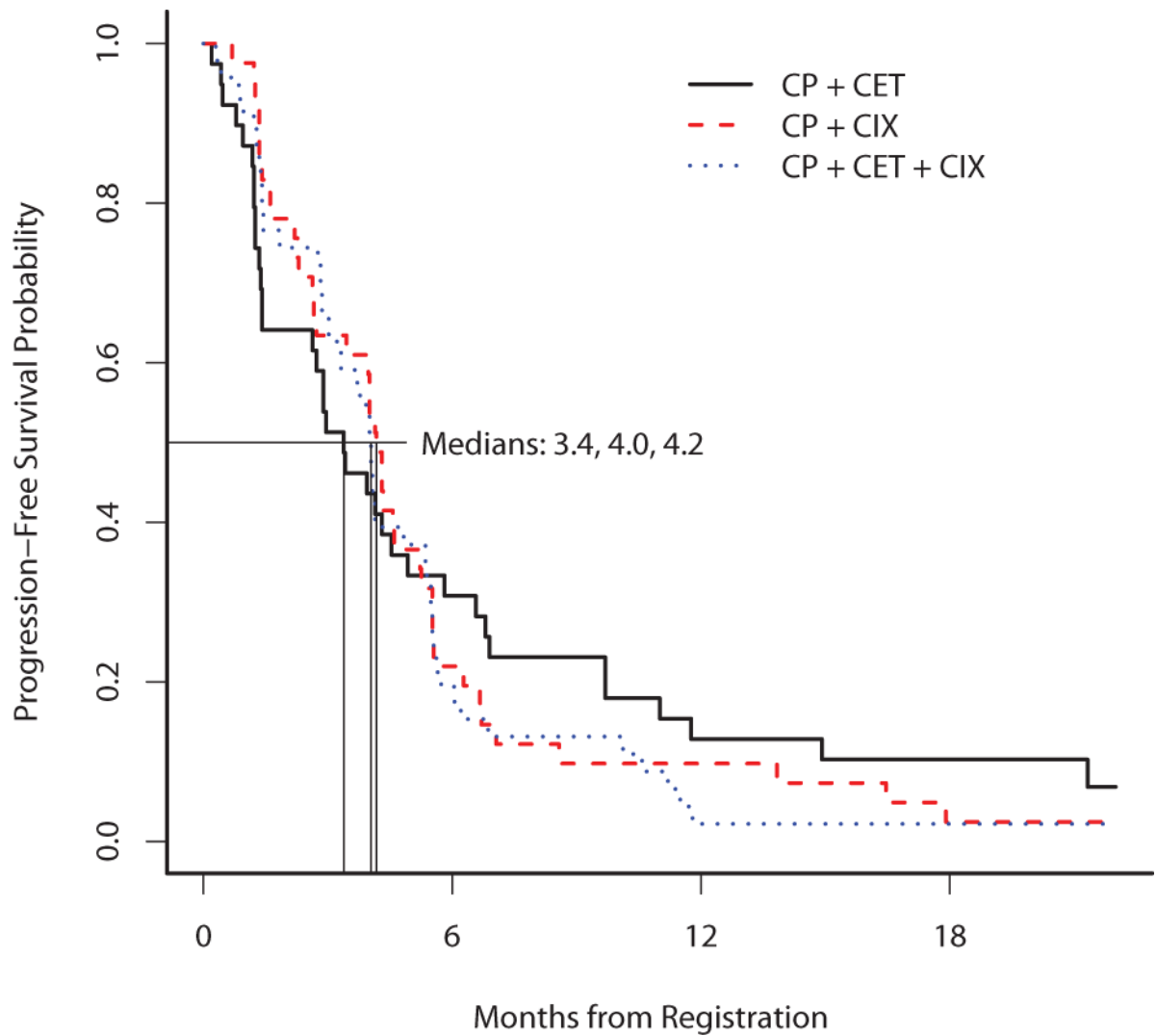


Figure 2. Progression-free survival

This figure provides the Kaplan-Meier curves for progression-free survival of the 3 arms

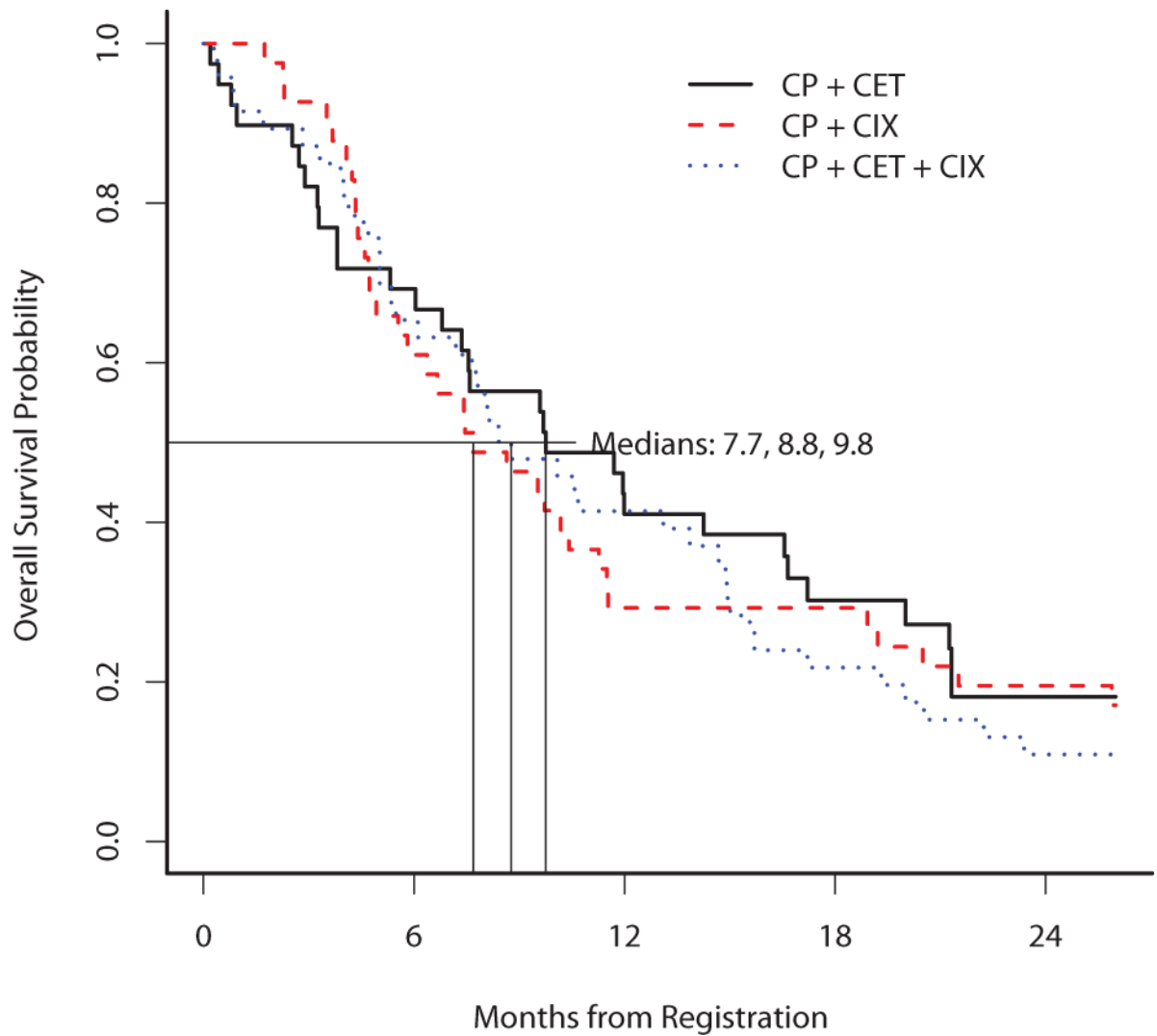


Figure 3. Overall survival

This figure provides the Kaplan-Meier curves for overall survival of the 3 arms

Table 1

Patient Demographics and Disease Characteristics by Treatment Arm

Variable	Category	Arm A	Arm B	Arm C	Total
Total (n)		39	41	47	127
Sex					
	Male	20(51)	24(59)	25(53)	69(54)
	Female	19(49)	17(41)	22(47)	58(46)
Race, n (%)					
	White	36(92)	34(83)	44(94)	114(90)
	Black	3(8)	6(15)	2(4)	11(9)
Age					
	Median (Min, Max)	60 (42, 89)	60 (43, 81)	60 (44, 76)	60 (42, 89)
PS					
	0	19(49)	22(54)	28(60)	69(54)
	1	20(51)	19(46)	19(40)	58(46)
Weight Loss					
	< 5	29(74)	31(76)	35(74)	95(75)
	5 - < 10	8(21)	5(12)	7(15)	20(16)
	10 - < 20	2(5)	5(12)	4(9)	11(9)
	> = 20	0(0)	0(0)	1(2)	1(1)
Smoking Status					
	Current Smoker	17(44)	19(46)	31(66)	67(53)
	Former Smoker	21(54)	19(46)	15(32)	55(43)
	Never Smoked	1(3)	3(7)	1(2)	5(4)
Stage					
	IIIB, not recurrent	1(3)	1(2)	1(2)	3(2)
	IV, not recurrent	34(87)	34(83)	44(94)	112(88)
	Recurrent	4(10)	6(15)	2(4)	12(9)
Histology					
	Squamous	11(28)	19(46)	21(45)	51(40)
	Adenocarcinoma	17(44)	11(27)	20(43)	48(38)
	Large cell	1(3)	0(0)	0(0)	1(1)
	BAC	2(5)	0(0)	0(0)	2(2)
	NOS	4(10)	7(17)	6(13)	17(13)
	Combined/Mixed	2(5)	2(5)	0(0)	4(3)
	Other	2(5)	2(5)	0(0)	4(3)
Liver					
	No	29(74)	30(73)	39(83)	98(77)
	Yes	9(23)	11(27)	7(15)	27(21)
	Unknown	1(3)	0(0)	1(2)	2(2)
Adrenal					
	No	33(85)	30(73)	34(72)	97(76)
	Yes	5(13)	11(27)	12(26)	28(22)
	Unknown	1(3)	0(0)	2(4)	2(2)
Bone					
	No	23(59)	29(71)	28(60)	80(63)
	Yes	14(36)	12(29)	17(36)	43(34)
	Unknown	2(5)	0(0)	2(4)	4(3)
Brain					
	No	36(92)	33(80)	40(85)	109(86)
	Yes	3(8)	8(20)	7(15)	18(14)

Table 2

Key Grade 3–5 Adverse Event Incidence, Any Attribution

Adverse Event Type	A (n=42)					B (n=44)					C (n=48)				
	Grade					Grade					Grade				
	3	4	5	3	4	5	3	4	5	3	4	5	3	4	5
Anemia	7	0	0	3	1	0	5	1	0						
Febrile neutropenia	3	0	0	2	0	0	2	0	0	2	0	0			
Fatigue	6	0	0	9	0	0	5	0	0						
Rash acneiform	2	0	0	0	0	0	4	0	0						
Diarrhea	0	0	0	1	0	0	4	0	0						
Nausea	5	0	0	3	0	0	4	0	0						
Vomiting	3	0	0	1	0	0	2	0	0						
Lung Infection	3	0	1	2	0	0	3	0	0						
Neutrophil count decreased	3	9	0	5	8	0	6	14	0						
Platelet count decreased	1	2	0	1	5	0	2	4	0						
Anorexia	3	0	0	4	0	0	2	0	0						
Dehydration	1	0	0	2	0	0	3	0	0						
Hyperglycemia	1	0	0	6	0	0	5	3	0						
Hyponatremia	1	0	0	2	0	0	8	0	0						
Arthralgia	3	0	0	4	0	0	3	0	0						
Myalgia	1	0	0	3	0	0	0	0	0						
Dyspnea	10	1	0	6	0	0	4	2	0						
Thromboembolic event	0	1	0	2	2	0	0	0	0						